



Reduced neutrophilic inflammation by inhalation of dry powder calcium salts in a mouse model of sub-chronic tobacco smoke exposure

RATIONALE: Inhaled dry powder (DP) calcium (Ca) salts exhibit anti-infective and anti-inflammatory efficacy in preclinical models. This multi-factorial mechanism that provides a novel approach to preventing acute exacerbations (AE) in COPD by targeting both underlying airway inflammation and the infectious cause of AEs. In sub-chronic mouse models of tobacco smoke (TS) exposure inhaled Ca salts reduce neutrophilic inflammation with effects comparable to a p38 MAP kinase inhibitor. The goal of this study was to further evaluate the efficacy of inhaled Ca salts in this model and to evaluate the effect of the therapy on chemokine and cytokine secretion. **METHODS:** C57BL6 mice were exposed to TS for 4d or 11d. Treatments with Ca-based DP (PUR118) were delivered by inhalation exposure. A p38 MAP kinase inhibitor (100µg/kg) was used as a positive control. Mice were euthanized either 4h or 24h after the last TS exposure. BAL cells, chemokines and cytokines were quantified and histopathology performed. **RESULTS:** In a 4d exposure model, treatment with PUR118 once daily 1h before TS reduced inflammatory cells [macrophages (52%) and neutrophils (62%)] compared to control DP ($p < 0.01$). Similar effects were observed when mice were treated 6h before each TS exposure, suggesting an extended duration of action. Anti-inflammatory efficacy correlated with significant reductions in key neutrophilic and pro-inflammatory chemokines and cytokines (e.g. KC and MIP2) in BAL. In an 11d exposure model, PUR118 reduced inflammation using both prophylactic and therapeutic dosing regimes. Treatment was associated with reduced tissue inflammation and a reduced severity of peri-vascular and peri-bronchiolar inflammation, bronchiolitis, alveolitis, and pneumonitis. **CONCLUSIONS:** PUR118 reduced TS induced inflammation and improved lung pathology with equivalent efficacy to the p38 MAP kinase inhibitor.